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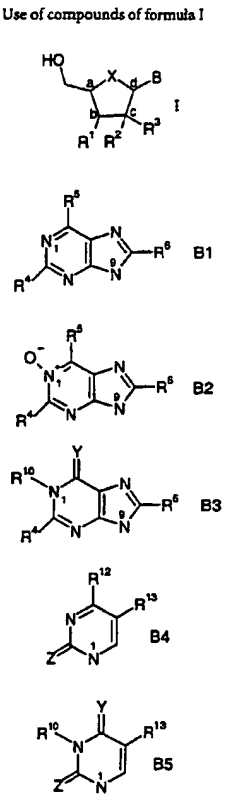
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,

[Continued on next page]

(54) Title: NUCLEOSIDE DERIVATIVES FOR THE TREATMENT OF HEPATITIS C



(57) Abstract: Use of compounds of formula (I), wherein R^1 is hydrogen, hydroxy, alkyl, hydroxyalkyl, alkoxy, halogen, cyano, isocyano or azido; R^2 is hydrogen, hydroxy, alkoxy, chlorine, bromine or iodine; R^3 is hydrogen; or R^2 and R^3 together represent $=CH_2$; or R^2 and R^3 represent fluorine; X is O, s or CH_2; a, b, c, d denoting asymmetric carbon atoms each of which is substituted with 4 different substituents; and B signifies a purine base B1 which is connected through the 9-nitrogen of formula (B1), wherein R^4 is hydrogen, hydroxyl, alkyl, alkoxy, alkylthio, aryloxy, arylthio, heterocyclyl, NR^7R^8, halogen or SH; R^5 is hydrogen, hydroxy, alkyl, haloalkyl, cycloalkyl, alkoxy, alkylthio, aryl, aryloxy, arylthio, heterocyclyl, heterocyclylamino, halogen, NR^7R^8, $NHOR^9$, $NHNR^7R^8$ or SH; R^6 is hydrogen, hydroxy, alkyl, alkoxy, alkylthio, aryloxy, arylthio, heterocyclyl, NR^7R^8, halogen, SH or cyano; R^7 and R^8 are independently of each other hydrogen, alkyl, aryl, hydroxyalkyl, alkenylalkyl, alkynylalkyl, cycloalkyl or acyl; R^9 is hydrogen, alkyl or aryl; or B signifies an oxidised purine base B2 which is connected through the 9-nitrogen of formula (B2), wherein R^4, R^5 and R^6 are as defined above; or B signifies a purine base B3 which is connected through the 9-nitrogen of formula (B3), wherein R^4 and R^6 are as defined above; R^{10} is hydrogen, alkyl or aryl; Y is O, S or NR^{11}; R^{11} is hydrogen, hydroxy, alkyl, OR^9, heterocyclyl or NR^7R^8; R^7, R^8 and R^9 are as defined above; or B signifies a pyrimidine base B4 which is connected through the 1-nitrogen of formula (B4), wherein Z is O or S; R^{12} is hydrogen, hydroxy, alkyl, alkoxy, haloalkyl, alkylthio, aryl, aryloxy, arylthio, heterocyclyl, heterocyclylamino, halogen, NR^7R^8, $NHOR^9$, $NHNR^7R^8$ or SH; R^{13} is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, cycloalkyl or halogen; R^7, R^8 and R^9 are as defined above; or B signifies a pyrimidine base B5 which is connected through the 1-nitrogen of formula (B5), wherein Y, Z, R^{10} are as defined above for the treatment of diseases mediated by the Hepatitis C Virus (HIV) or for the preparation of a medicament for such treatment. The invention is concerned with novel and known purine and pyrimidine nucleoside derivatives, their use as inhibitors of subgenomic Hepatitis C Virus (HCV) RNA replication and pharmaceutical compositions of such compounds.

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CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

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Published:

— *with international search report*

(88) Date of publication of the international search report:
14 November 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H19/06 C07H19/16 A61K31/7064 A61K31/7076 A61P31/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 01443 A (WELLCOME FOUND ;KOSZALKA GEORGE WALTER (US); DRAANEN NANINE AGNETA) 20 January 1994 (1994-01-20) examples claims page 3, paragraph 3 ---	1,2,5,6, 8
X	WO 98 16184 A (ICN PHARMACEUTICALS ;AVERTT DEVERON (US); TAM ROBERT (US); WANG GU) 23 April 1998 (1998-04-23) examples claims page 11, line 14 ---	1,15,16

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 July 2002	26. 07. 2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	de Nooy, A

INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 55 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

2. [X] Claims Nos.: 43,49-57 (all partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT, no additional fees are to be refunded.

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[X] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 43,49-57 (all partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty for claim 43. So many documents were retrieved that it is impossible to determine which parts of the claim may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, it appears impossible to execute a meaningful search and/or to issue a complete search report over the whole breadth of the claims. Consequently, the search and the report for this claim has been restricted to the case where R13''''' is an alkyl but not methyl.

Present claims 49-57 relate to an extremely large number of compounds. In fact, the claims contain so many options, that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the above mentioned claims have been searched insofar as the compounds of claim 49 fall within earlier compound claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1 (in part), 3-4 (in part), 12-13 (in part), 14, 34, 35, 50-56 (in part)

   Compounds of Formula I-a of claim 34 where B' = B2-a of claim 34, and uses, compositions and processes pertaining thereto.

2. Claims: 1 (in part), 3-4 (in part), 15-16 (in part), 17, 36, 37, 50-56 (in part)

   Compounds of Formula I-b of claim 36 where B'' = B3-a of claim 36, and uses, compositions and processes pertaining thereto.

3. Claims: 1-4 (in part), 18-25 (in part), 26, 27-28 (in part), 29, 38-42, 50-56 (in part)

   Compounds of Formula I-c of claim 38 where B''' = B4-a of claim 38, compounds of Formula I-d of claim 40 where B'''' = B4-b of claim 40 or 41, and uses, compositions and processes pertaining thereto.

4. Claims: 1-4 (in part), 30-32 (in part), 33, 43-48, 50-56 (in part)

   Compounds of Formula I-e of claim 43 where B''''' = B5-a of claim 43, compounds of Formula I-f of claim 45 where B'''''' = B5-b of claim 45, compounds of Formula I-g of claim 47 where B''''''' = B5-c of claim 47 and uses, compositions and processes pertaining thereto.

5. Claims: 1-4 (in part), 5-10, 12-13 (in part), 15-16 (in part), 18-25 (in part), 27-28 (in part), 30-32 (in part), 55-56 (in part)

   Use of compounds of the above mentioned claims which do not fall within one of the previous subjects for the treatment of Hepatitis C Virus or for the preparation of a medicament for such treatment.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/09633

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 05687 A (UNIV BIRMINGHAM ;WELLCOME FOUND (GB); MILLER JOHN ALLEN (GB); YOUN) 17 March 1994 (1994-03-17) examples claims page 4, line 22 - line 36	1,2, 30-32
A	EP 0 468 352 A (NIPPON KAYAKU KK) 29 January 1992 (1992-01-29) examples claims page 14, line 17	1
X	US 5 102 873 A (MONTGOMERY JOHN A ET AL) 7 April 1992 (1992-04-07) example 3	34
X	US 4 755 594 A (BRIDGES ALEXANDER J ET AL) 5 July 1988 (1988-07-05) example 4	34
X	P.J.M. VAN GALEN ET AL.: "A binding site model and structure-activity relationships for the rat A3 adenosine receptor" MOLECULAR PHARMACOLOGY, vol. 45, 1994, pages 1101-1111, XP008000722 compound 30	34
A	US 5 998 387 A (SCAMMELLS PETER J ET AL) 7 December 1999 (1999-12-07) figure 2	34
A	K. MIURA ET AL.: "Chemical conversion of adenosine to guanosine (Nucleosides and nucleotides. XI)" CHEM. PHARM. BULL., vol. 23, 1975, pages 464-466, XP002190612 chart 1	34
X	W.M. HAMMARGREN ET AL.: "Identification of a novel nucleoside, 1,N6-dimethyladenosine, in human cancer urine" ANALYTICA CHIMICA ACTA, vol. 247, 1991, pages 201-209, XP008005307 compound 1	36
X	US 3 891 623 A (VORBRUGGEN HELMUT ET AL) 24 June 1975 (1975-06-24) examples 2,3	38

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	H. VORBRÜGGEN ET AL.: "Eine neue einfache Synthese von Cytidinen" LIEBIGS ANN. CHEM., 1975, pages 988-1002, XP002204034 compound 19	38
X	X.-X. ZHOU ET AL.: "Pyridyl groups for protection of the imide functions of uridine and guanosine. Exploration of their displacement reactions for site-specific modifications of uracil and guanine bases" ACTA CHEMICA SCANDINAVICA B, vol. 40, 1986, pages 806-816, XP002204035 the whole document	38
X	R.W. MILES ET AL.: "Nucleic acid related compounds. 87. Nucleophilic functionalization of cytidine and 2'-deoxycytidine derivatives via elaboration of the 4-amino group into a readily displaced 1,2,4-triazol-4-yl substituent" J. ORG. CHEM., vol. 60, 1995, pages 7066-7069, XP002204036 compounds 3,4	38
X	G.E. KEYSER ET AL.: "Iodomethylethers from 1,3-dioxolane and 1,3-oxothiolane: preparation of acyclic nucleoside analogs" TETRAHEDRON LETTERS, 1979, pages 3263-3264, XP002204037 compound 3	38
X	US 4 526 988 A (HERTEL LARRY W) 2 July 1985 (1985-07-02) the whole document	40
X	HERTEL L W: "SYNTHESIS OF 2-DEOXY-2,2-DIFLUORO-D-RIBOSE AND 2-DEOXY-2,2-DIFLUORO-D-RIBOFURANOSYL NUCLEOSIDES" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 53, no. 11, 27 May 1988 (1988-05-27), pages 2406-2409, XP000572745 ISSN: 0022-3263 the whole document	40

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHOU T S ET AL: "STEREOSPECIFIC SYNTHESIS OF 2-DEOXY-2,2-DIFLUORORIBONOLACTONE AND ITS USE IN THE PREPARATION OF 2'-DEOXY-2'.2'-DIFLUORO-BETA-D-RIBOFURANOSYL PYRIMIDINE NUCLEOSIDES: THE KEY ROLE OF SELECTIVE CRYSTALLIZATION" SYNTHESIS, GEORG THIEME VERLAG. STUTTGART, DE, no. 6, 1 June 1992 (1992-06-01), pages 565-570, XP000572747 ISSN: 0039-7881 compounds 1,16 ---	40
X	KOTRA L P ET AL: "STRUCTURE-ACTIVITY RELATIONSHIPS OF 2'-DEOXY-2',2'-DIFLUORO-L-ERYTHRO-PENTOFURANOSYL NUCLEOSIDES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 40, no. 22, 1997, pages 3635-3644, XP000867642 ISSN: 0022-2623 compounds 43-52 ---	40
X	KOTRA L P ET AL: "Synthesis of 2,3-dideoxy-2,2-difluoro-l-glycero-pentofuranosyl nucleosides" CARBOHYDRATE RESEARCH, ELSEVIER SCIENTIFIC PUBLISHING COMPANY. AMSTERDAM, NL, vol. 306, no. 1-2, January 1998 (1998-01), pages 69-80, XP004204788 ISSN: 0008-6215 scheme 1 ---	40
X	M. SEKINE, T. NAKANISHI: "Facile synthesis of 3'-O-methylthymidine and 3'-deoxythymidine and related deoxygenated thymidine derivative: A new method for selective deoxygenation of secondary hydroxy groups" J. ORG. CHEM., vol. 55, 1990, pages 924-928, XP002204038 compound 2 ---	43
X	A. HAMPTON ET AL.: "Species- or Isozyme-specific enzyme inhibitors. 5. Differential effects of thymidine substituents on affinity for rat thymidine kinase isozymes" J. MED. CHEM., vol. 25, 1982, pages 644-649, XP002204039 compounds 7d,e ---	43

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	S. EL-KOUSY ET AL.: "Synthesis and investigation of antiviral activity of 3'-O-(aminoalkyl)-thymidines and their quarternary ammonium salts" MONATSHEFTE FÜR CHEMIE, vol. 125, 1994, pages 713-721, XP002204040 compounds 4a-d, 6a-d	43
X	N.K. KOCHETKOV ET AL.: "The mechanism of the reaction of hydroxylamine and O-methylhydroxylamine with cytidine" TETRAHEDRON LETTERS, 1967, pages 3253-3257, XP002204041 compound 4a	47,48
E	WO 01 90121 A (NOVIRIO PHARMACEUTICALS LTD ;UNI DEGLI STUDI DI CAGLIARI (IT); LAC) 29 November 2001 (2001-11-29) the whole document	1-57

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/09633

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9401443 A	20-01-1994	AU 4508593 A	31-01-1994
		CA 2139132 A1	20-01-1994
		CN 1087089 A	25-05-1994
		EP 0648218 A1	19-04-1995
		WO 9401443 A1	20-01-1994
		JP 7508531 T	21-09-1995
		MX 9303985 A1	28-02-1994
		ZA 9304742 A	03-01-1995
WO 9816184 A	23-04-1998	AU 727177 B2	07-12-2000
		AU 4899997 A	11-05-1998
		BR 9714349 A	14-11-2000
		CA 2322053 A1	16-07-1998
		CA 2323791 A1	23-04-1998
		CN 1286258 A	07-03-2001
		CN 1296011 A	23-05-2001
		CN 1233254 A	27-10-1999
		CZ 9901267 A3	14-07-1999
		EP 1072607 A2	31-01-2001
		EP 0961775 A2	08-12-1999
		HU 0001186 A2	28-05-2001
		JP 2001524936 T	04-12-2001
		JP 2002105096 A	10-04-2002
		NO 991784 A	15-06-1999
		NO 20004326 A	15-06-1999
		NO 20004328 A	15-06-1999
		NZ 505531 A	31-08-2001
		NZ 505553 A	30-11-2001
		NZ 505554 A	30-11-2001
		PL 332694 A1	27-09-1999
		SI 20024 A	29-02-2000
		SK 48199 A3	18-01-2000
		US 2002058635 A1	16-05-2002
		WO 9816184 A2	23-04-1998
		AU 736075 B2	26-07-2001
		AU 6023898 A	03-08-1998
		BR 9807473 A	21-03-2000
		CN 1312254 A	12-09-2001
		CN 1289594 A	04-04-2001
		CN 1253504 T	17-05-2000
		EP 1103559 A1	30-05-2001
		EP 0998293 A1	10-05-2000
		HU 0001526 A2	28-05-2001
		JP 2002515892 T	28-05-2002
		JP 2002080490 A	19-03-2002
		NO 993439 A	13-09-1999
		NO 20004327 A	13-09-1999
		NO 20004329 A	13-09-1999
		PL 336579 A1	03-07-2000
		SI 9820003 A	30-06-1999
		SK 94099 A3	11-06-2001
		WO 9830223 A1	16-07-1998
WO 9405687 A	17-03-1994	AU 4973393 A	29-03-1994
		CA 2143834 A1	17-03-1994
		EP 0658166 A1	21-06-1995
		WO 9405687 A1	17-03-1994
		JP 8504753 T	21-05-1996

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/09633

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0468352 A	29-01-1992	AU 642031 B2	07-10-1993
		AU 8125391 A	30-01-1992
		CA 2047644 A1	25-01-1992
		CN 1059524 A ,B	18-03-1992
		EP 0468352 A2	29-01-1992
		JP 5001044 A	08-01-1993
		US 5374625 A	20-12-1994
US 5102873 A	07-04-1992	NONE	
US 4755594 A	05-07-1988	AU 592728 B2	18-01-1990
		AU 6797287 A	06-08-1987
		CA 1270821 A1	26-06-1990
		DK 46687 A	01-08-1987
		EP 0232813 A2	19-08-1987
		FI 870371 A	01-08-1987
		KR 9100602 B1	28-01-1991
		NO 870390 A ,B,	03-08-1987
		NZ 219128 A	29-01-1990
		PH 23342 A	14-07-1989
		PT 84226 A ,B	01-02-1987
		JP 62228095 A	06-10-1987
		ZA 8700120 A	31-08-1988
US 5998387 A	07-12-1999	US 5736528 A	07-04-1998
		US 5631260 A	20-05-1997
		US 5446046 A	29-08-1995
		AU 728439 B2	11-01-2001
		AU 1522097 A	28-07-1997
		BR 9612324 A	28-12-1999
		CA 2238736 A1	10-07-1997
		EP 1019426 A1	19-07-2000
		JP 2000502712 T	07-03-2000
		NZ 326608 A	28-04-2000
		NZ 502628 A	29-06-2001
		WO 9724363 A1	10-07-1997
		US 5668139 A	16-09-1997
		AT 187726 T	15-01-2000
		AU 699630 B2	10-12-1998
		AU 1044995 A	22-05-1995
		CA 2172726 A1	04-05-1995
		DE 69422191 D1	20-01-2000
		DE 69422191 T2	25-05-2000
		DK 725782 T3	13-06-2000
		EP 0725782 A1	14-08-1996
		ES 2141913 T3	01-04-2000
		GR 3032730 T3	30-06-2000
		JP 9507052 T	15-07-1997
		JP 2002105094 A	10-04-2002
		PT 725782 T	31-05-2000
		WO 9511904 A1	04-05-1995
US 3891623 A	24-06-1975	DE 2122991 A1	16-11-1972
		BE 783026 A1	06-11-1972
		CH 579585 A5	15-09-1976
		CS 171723 B2	29-10-1976
		FR 2135249 A5	15-12-1972
		GB 1395764 A	29-05-1975

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/09633

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3891623 A		NL 7206058 A	07-11-1972
US 4526988 A	02-07-1985	AT 29726 T	15-10-1987
		AU 565856 B2	01-10-1987
		AU 2537484 A	13-09-1984
		BG 40814 A3	16-02-1987
		CA 1218647 A1	03-03-1987
		CA 1223869 C	07-07-1987
		CS 246075 B2	16-10-1986
		CY 1489 A	08-12-1989
		DD 216468 A5	12-12-1984
		DE 3466224 D1	22-10-1987
		DK 114484 A ,B,	11-09-1984
		DK 190590 A	10-08-1990
		EP 0122707 A1	24-10-1984
		ES 530364 D0	01-12-1985
		FI 840890 A ,B,	11-09-1984
		GB 2136425 A ,B	19-09-1984
		GB 2172287 A ,B	17-09-1986
		GR 81845 A1	12-12-1984
		HK 44989 A	09-06-1989
		HU 193893 B	28-12-1987
		IE 57071 B1	22-04-1992
		IL 71143 A	31-07-1988
		IL 80463 A	31-07-1988
		JP 1986188 C	08-11-1995
		JP 6009602 A	18-01-1994
		JP 6102655 B	14-12-1994
		JP 1833350 C	29-03-1994
		JP 5042438 B	28-06-1993
		JP 59175498 A	04-10-1984
		KE 3874 A	30-06-1989
		KR 8601283 B1	05-09-1986
		LU 88791 A9	05-11-1996
		MX 9203246 A1	31-07-1992
		NZ 207358 A	06-03-1987
		PH 23240 A	06-06-1989
		PH 23593 A	11-09-1989
		PL 246601 A1	13-08-1985
		PT 78181 A ,B	01-04-1984
		RO 89963 A1	30-09-1986
		SG 21889 G	14-07-1989
		SU 1442076 A3	30-11-1988
		US 4808614 A	28-02-1989
		US 5015743 A	14-05-1991
		US 5118820 A	02-06-1992
		US 4692434 A	08-09-1987
		ZA 8401605 A	30-10-1985
WO 0190121 A	29-11-2001	AU 7490601 A	03-12-2001
		WO 0190121 A2	29-11-2001